REMARKS

The amendments above correct errors in the claims. Claims 1-3 and 6-14 have not been narrowed in scope by these amendments.

Restriction

Applicants acknowledge the separate classification of the subject matter within Groups I, II and III but submit that the subject matter of these claims is linked by a common structure and should be examined together, absent an undue burden on the Examiner. This common structure includes (a) a urea functional group, (b) two cyclic (aryl/hetaryl) structures bound to each side of the urea functional group and (c) one of these cyclic structures is a hetaryl ring substituted at the 2 position by another aryl or hetaryl ring. The Examiner has identified only one subclass for each group. While the size of these subclasses may be substantial, it is not clear on the record a search all three subclasses could be an undue burden. Therefore, Applicants submit the requirement to restrict the application should be withdrawn. In the absence of such a withdrawal, Applicants affirm the election of Group I drawn to compounds of Formula I wherein A is pyrazolyl.

Applicants acknowledge the reminder that inventorship may have to be amended if cancellation of claims to a non-elected invention becomes necessary.

Priority

Applicants appreciate the notice from the Examiner that the first paragraph in the specification requires amendment to correcting claim priority. This paragraph has been amended above.

Oath/Declaration

Applicants will attend to providing a new oath once issues relating to amendments to inventorship are settled.

Specification

A new Abstract has been provided.

Claim Rejections

Applicants maintain that claims 1-8 and 15-25 are not drawn to an improper Markush group. The species of the Markush Group are linked by common structural elements as discussed above with respect to the restriction requirement. One skilled in the art would recognize the ureas defined therein as having similarities. Therefore, grouping these compounds in one claim is not improper.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner's attention is drawn to the recent board decision; Ex Parte Henning Böttchen Appeal No. 1998-1487, Serial No. 08/628,250, where a method claim was found to satisfy 35 U.S.C. §112, first paragraph although it defined illnesses to be treated as "an illness associated with such activity."

The term "disease mediated by raf kinase" is similar. The activity of the compound administered is clearly defined and the disease defined by this activity is specifically defined. Those skilled in the art would clearly recognize what is intended, as is evident by the numerous publications cited in the Background of the Invention.

Applicants do not claim these compounds treat all cancers, only those mediated by raf kinase.

Applicants submit the identification of these compounds as inhibitors of raf kinase is sufficient to enable one skilled in the art know how to use them. Compounds with such activity are well known in the art and appropriate dosages and method of administration can be determined by the guidance provided on pages 14-17.

35 USC §112, second paragraph

The claims have been amended in response to these rejections. The examiner's recognition and identification of these errors are appreciated.

Rejection Under 35 U.S.C. §102 (e)

Applicants traverse the rejection under 35 U.S.C. §102(e) based on Regan (U.S. Patent 6,080,763). The priority document (provisional application serial number 60/064,102) for this

reference does not have the example relied on. The filing date for the patent (U.S. 6,080,763) is subsequent to the filing date of this application. Therefore, the disclosure relied on in making this rejection is not prior art and the rejection should be withdrawn.

Rejection Under 35 U.S.C. §102(e)/35 U.S.C. §103(a)

Applicants traverse the rejection of claims 1-10 and 24-25 under 35 U.S.C. §102(e), or in the alternative under 35 U.S.C. §103(a) in view of Regan et al., (U.S. Patent No. 6,080,763). This rejection relies on the generic formula in col. 6 of the patent which is found in the provisional application. However, this generic formula can be calculated to cover over 96 different heterocycles and the substituents therefore, such as R^3, have multiple values. Therefore, this generic formula alone is insufficient to render the claimed compounds obvious consistent with the holding in the case of In Re Baird 29 USPQ2d 1550 (Fed Circuit 1994).

The specific pyrazolyl structure on page 8 of the provisional application includes the substituent R^4 which is inconsistent with the compounds claimed herein. While this substituent can be hydrogen, multiple variables at this location as well as the multiple variables for R^3 and R^1 provide no direction for one skilled in the art to arrive at the compounds claimed herein.

The specific pyrazole compounds described on page 9 of the provisional application do not have the same 2,5-substituent pattern of the ureas claimed herein such as those exemplified in the tables in this application. In that the disclosure of the provisional application would not lead one skilled in the art to the compounds claimed herein, Applicants submit that the 35 U.S.C. §102(e)/103(a) rejection based on Regan U.S. 6,080,763 should be withdrawn.

Creswell (U.S. Patent 5,162,360)

Reference is made to the generic formula at col. 2 and the structures and substituents in col. 3. of Creswell (U.S. 5,162,360) to support the rejection of claims 1-5, 7-10 and 24-25 under 35 U.S.C. §103(a). This broad generic disclosure provides no direction to prepare the compounds having both the alkyl and the aryl/hetaryl substituents requirements of the compounds of the present invention. For example, the substituent definition for R^{11} includes aryl and hetaryl and also hydrogen, i.e. unsubstituted at the 2-position. In addition, the substituent definitions for R^{10} at the 5-position include an alkyl amine as well as the short chain alkyl groups excluded by Applicants range of C_3 to C_{10} alkyl.

The compound in Example 24 of Creswell also does not lead one skilled in the art to the compounds of the present invention in that the alkyl substituent at the 5 position (dodecyl) contains more carbon atoms (12) than permitted in the compounds claimed herein. Applicants claim a range of C_3 to C_{10} alkyl for the substituent at the 5 position.

Based on the above remarks, Applicants submit that all pending claims are in condition for allowance and therefore, withdrawal of the rejections and allowance of these claims are earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please amend the first paragraph on page 1 to read as follows:

This Application is a continuation of Serial No. 09/303,621 filed on December 22, 1998, ~~which is a continuation-in-part of Serial No. 60.126,439 which was converted from Serial No. 08/996,184~~ This application claims priority of provisional application Serial No. 60/126,439 filed December 22, 1997.

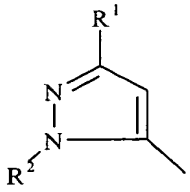
IN THE CLAIMS

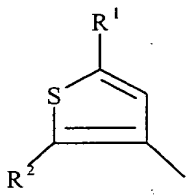
Please amend claims 1, 3, 4-5, 15, 17-19 and 24-25 as follows.

1. A compound of formula I ~~and~~ or a pharmaceutically acceptable ~~salts~~ salt thereof

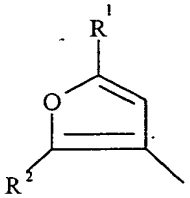
A-NH-C-NH-B I

wherein A is a heteroaryl selected from the group consisting of





and



wherein R^1 is selected from the group consisting of C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl;

B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, -CO_2R^5, -$C(O)NR^5R^{5'}$, -$C(O)R^5$, -NO_2, -OR^5, -SR^5, -$NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_2-

C_{10} alkenyl, substituted C_1-C_{10} alkoxyl, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to perhalosubstituted C_2-C_{10} alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is -O-, -S-, $-N(R^5)$-, $-(CH_2)_m$-, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-NR^5C(O)NR^5R^{5'}$-, $-NR^5C(O)$-, $-C(O)NR^5$-, $-O(CH_2)_m$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$-, $-CX^a_2$-, $-S-(CH_2)_m$- and $-N(R^5)(CH_2)_m$-,

m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-C(O)R^5$, $NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$, and

wherein R^2 is C_6-C_{14} aryl, C_3-C_{14} heteroaryl, substituted C_6-C_{14} aryl or substituted C_3-C_{14} heteroaryl,

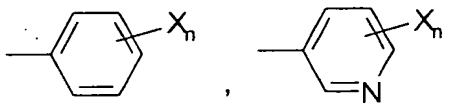
wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

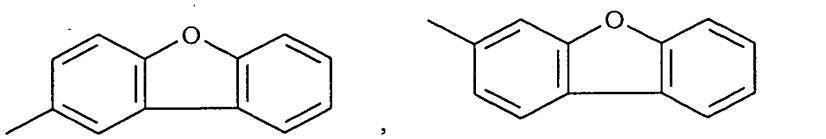
wherein n = 0-3 and each V is independently selected from the group consisting of -CN, -CO_2R^5, -$C(O)NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5R^{5'}$, -$C(O)R^5$, -$OC(O)NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -SO_2R^5, -SOR^5, -$NR^5C(O)R^{5'}$, -NO_2, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

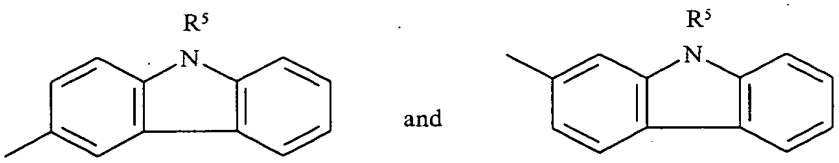
where if V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, -CO_2R^5, -$C(O)R^5$, -$C(O)NR^5R^5$, -$NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5C(O)R^{5'}$, -$NR^5C(O)OR^{5'}$ and -NO_2;

wherein R^5 and $R^{5'}$ are each independently as defined above.

3. (Amended) A compound of claim 2, wherein B is up to a tricyclic aromatic ring structure selected from the group consisting of







;

which is <u>unsubstituted or</u> substituted ~~or unsubstituted~~ by halogen, up to per-halosubstitution, and wherein

n = 0-3 and

each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_{1-10}-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, and substituted C_1-C_{10} alkyl, substituted C_{2-10}-alkenyl, substituted C_{1-10}-alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_{2-10}-alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

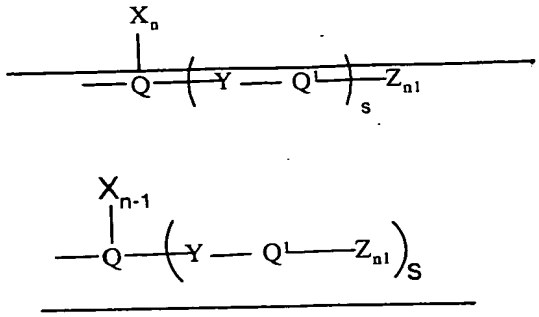
wherein Y is - O-, -S-, $-N(R^5)-$, $-(CH_2)-_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-NR^5C(O)NR^5R^{5'}-$, $-NR^5C(O)-$, $-C(O)NR^5-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$,

m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halo substitution and optionally substituted by Z_{n1}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$,

$-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl; wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$.

4. (Amended) A compound of claim 1, wherein B is



wherein

Y is selected from the group consisting of –O-, -S-, $-CH_2-$, $-SCH_2-$, $-CH_2S-$, -CH(OH)-, -C(O)-, $-CX^a_2$, $-CX^aH-$, $-CH_2O-$ and $-OCH_2-$,

X^a is halogen,

Q is a six member aromatic structure containing 0–2 nitrogen, unsubstituted or substituted ~~or unsubstituted~~ by halogen, up to per-halosubstitution;

Q^1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or ~~unsubstituted~~ substituted by halogen up to per-halosubstitution,

X, Z, n and n1 are as defined in claim 1, and s = 0 or 1.

5. (Amended) A compound of claim 4, wherein

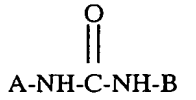
Q is phenyl or pyridinyl, ~~substituted or~~ unsubstituted or substituted by halogen, up to per-halosubstitution,

Q^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, ~~substituted or~~ unsubstituted or substituted by halogen, up to per-halo substitution, or Y-Q^1 is phthalimidinyl ~~substituted or~~ unsubstituted or substituted by halogen up to per-halo substitution, and

Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group

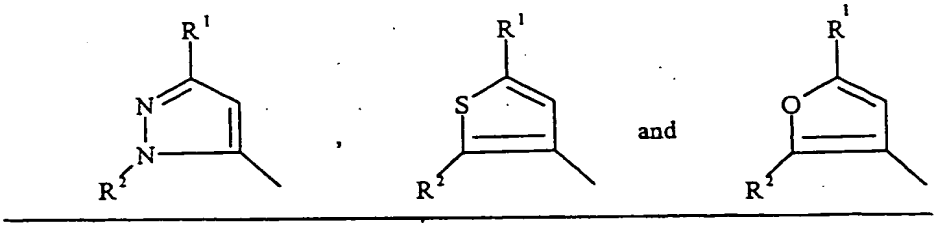
consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

15. (Amended) A method for the treatment of disease mediated by raf kinase, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof:

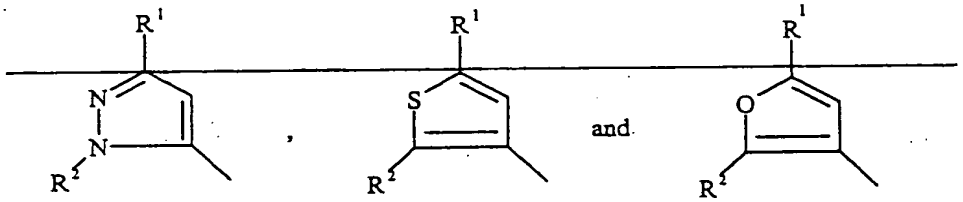


I

wherein A is a heteroaryl selected from the group consisting of



wherein R^1 is selected from the group consisting of C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl;



B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, CO_2R^5, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, $C_{2\text{-}10}$-alkenyl, $C_{1\text{-}10}$-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted $C_{2\text{-}10}$-

alkenyl, substituted C_{1-10}-alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_{2-10}-alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl, wherein Y is - O-, -S-, $-N(R^5)$-, $-(CH_2)-_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$-, $-CX^a_2$-, -S-$(CH_2)_m$- and $-N(R^5)(CH_2)_m$-,

m = 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-C(O)R^5$, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$, and

wherein R^2 is C_6-C_{14} aryl, C_3-C_{14} heteroaryl, substituted C_6-C_{14} aryl or substituted C_3-C_{14} heteroaryl,

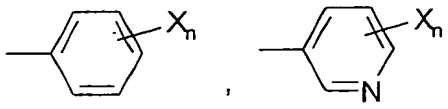
wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

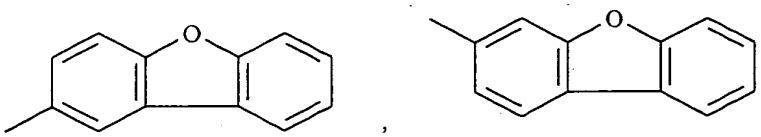
wherein n = 0-3 and each V is independently selected from the group consisting of -CN, -CO_2R^5, -$C(O)NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5R^{5'}$, -$OC(O)NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$NR^5C(O)OR^{5'}$, -SO_2R^5, -SOR^5, -$NR^5C(O)R^{5'}$, -NO_2, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

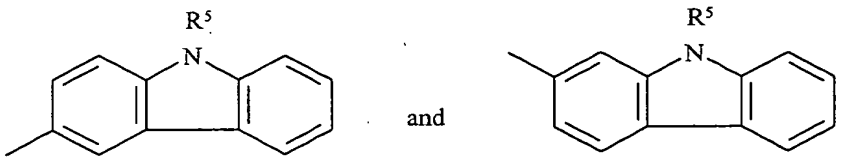
where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, -CO_2R^5, -$C(O)R^5$, -$C(O)NR^5R^5$, -$NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5C(O)R^{5'}$, -$NR^5C(O)OR^{5'}$ and -NO_2,

wherein R^5 and $R^{5'}$ are each independently as defined above.

17. (Amended) A method as in claim 15, wherein B is up to a tricyclic aromatic ring structure selected from the group consisting of







which is ~~substituted or~~ unsubstituted or substituted by halogen, up to per-halosubstitution, and wherein

n = 0-3 and

each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_{1-10}-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, and substituted C_1-C_{10} alkyl, substituted C_{2-10}-alkenyl, substituted C_{1-10}-alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

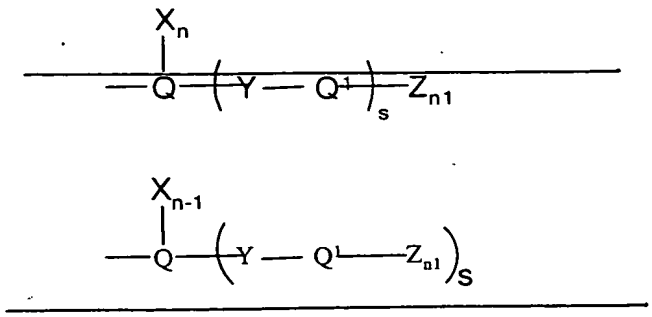
wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_{2-10}-alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is - O-, -S-, $-N(R^5)-$, $-(CH_2)-_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-NR^5C(O)NR^5R^{5'}-$, $-NR^5C(O)-$, $-C(O)NR^5-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$,

m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-C(O)R^5$, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl; wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$.

18. (Amended) A method of claim 15, wherein B is



wherein

Y is selected from the group consisting of –O-, -S-, $-CH_2-$, $-SCH_2-$, $-CH_2S-$, -CH(OH)-, -C(O)-, $-CX^a_2$, $-CX^aH-$, $-CH_2O-$ and $-OCH_2-$,

X^a is halogen,

Q is a six member aromatic structure containing 0–2 nitrogen, ~~substituted or~~ unsubstituted or substituted by halogen, up to per-halosubstitution;

Q^1 is a mono- or bicyclic aromatic structure of 3 to 10 carbon atoms and 0-4 members of the group consisting of N, O and S, unsubstituted or ~~unsubstituted~~ substituted by halogen up to per-halosubstitution,

X, Z, n and n1 are as defined in claim 15, and s = 0 or 1.

19. (Amended) A method as in claim 18, wherein

Q is phenyl or pyridinyl, ~~substituted or~~ unsubstituted or substituted by halogen, up to per-halosubstitution,

Q^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, or $Y-Q^1$ is phthalimidinyl substituted or unsubstituted by halogen up to per-halo substitution, and

Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group

consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen ~~or~~ up to per-halosubstitution.

24. (Amended) A pharmaceutical composition comprising <u>an effective amount</u> of a compound of claim 1 and a pharmaceutically acceptable carrier.

25. (Amended) A pharmaceutical composition comprising <u>an effective amount</u> of a compound of claim 2 and a pharmaceutically acceptable carrier.

ABSTRACT

The compounds are aryl and heteroaryl substituted heterocyclic ureas of the formula A-NH-C(O)-NH-B where A is the aryl or hetaryl substituted heterocyclic group and B is an aryl or heteroaryl moiety. The compounds inhibit raf kinase and are useful in the treatment of RAF kinase mediated diseases.